REMARKS

I. Status of the Claims

Claims 47-62 are currently pending, with claims 50-52, 56-58, 60-62 withdrawn from consideration as directed to a non-elected invention. Upon entry of this amendment, claim 47 is amended without prejudice or disclaimer. Applicants reserve the right to reintroduce the unamended claim in this or another application. Claims 47-62 thus remain pending following entry of this amendment, with claims 50-52, 56-58, 60-62 withdrawn from consideration.

II. Objections to the Specification

The PCT application number that was not available for the PCT application listed on page 13, line 16 of the specification has been inserted as requested. This amendment introduces no new matter.

III. Claim Rejections under 35 U.S.C. §112 - Written Description

Claims 47-59 and 54-55 stand rejected because the claims allegedly include subject matter that has not been adequately described such that one of ordinary skill could conclude that the claimed invention was in the possession of the inventors at the time the application was filed. The primary concern expressed in the Office Action is that the specification does not contain a disclosure that provides the identity of ligands that can be used to identify different CMV mutations.

It appears that the Examiner has misunderstood the nature of the invention. The invention does not involve the use of different ligands, each of which recognizes a different CMV mutation to detect the presence and/or absence of a mutation. Rather, as clarified in amended claim 47, the currently claimed invention involves collecting CMV and/or at least one CMV infected cell from a patient infected with CMV using a compound that binds CMV and/or a CMV infected cell. A segment of the CMV genome obtained from the collected CMV or CMV infected cell is then analyzed to detect the presence and/or absence of a mutation in the CMV genome. The analysis to detect the presence and/or absence of mutation can be performed

using a variety of nucleic acid sequence analysis techniques including, for example, those methods listed at page 22, lines 3-8.

It is thus submitted that the specification does adequately describe the current claims commensurate with the scope of the currently pending claims. The specification, for instance, provides an extensive list of compounds that could be used to bind CMV or a CMV infected cell (see, e.g., page 18, line 8 to page 21, line 19). As just noted, the application also provides several examples of techniques that could be used to analyze a segment of the CMV genome obtained from the collected CMV or CMV collected cells to detect the presence and/or absence of a mutation. This information is sufficient such that one of ordinary skill in the art could reasonably conclude that the inventors were in possession of the currently claimed invention.

IV. Claim Rejections under 35 U.S.C. §112 -- Enablement

Claims 47-49, 52-55 and 59 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to describe the claimed subject matter in sufficient detail such that one of ordinary skill could practice the claimed invention without undue experimentation. The Office Action lists a number of specific concerns that are addressed in turn below.

The first concern expressed in the Office Action is that the specification has not shown how a compound can differentiate between wild type and mutated CMV. This concern is the same as that raised with respect to the written description rejection and has been fully addressed in that section.

A second issue raised is that the compounds may bind pathogens other than CMV, which, if it occurred, could complicate the analysis. In response, Applicants initially note that the Patent Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention (see, e.g., MPEP 2164.04). Furthermore, the courts have held that when a rejection is made based upon the conclusion that specification fails to teach how to make and use the claimed invention that the Patent Office must "back up assertions of its own with acceptable evidence or reasoning" (see, e.g., Id.). Here the Patent Office has not provided

any evidence or rationale to justify its conclusion that the compounds that bind CMV or CMV infected cells will bind other pathogens and, as such, has not satisfied its burden of demonstrating lack of enablement with respect to this particular issue.

Even if a compound did bind a pathogen in addition to CMV as the Office speculates, this still would not mean that the claimed invention lacks enablement. Because the sequence of the CMV genome was known as of the priority date of the instant application (see, e.g., page 5, lines 23-34), one of ordinary skill in the art would readily recognize if the nucleic acid was from a source other than CMV when analyzing the collected nucleic acid obtained in step (b). Additionally utilizing certain nucleic acid analysis techniques recommended in the specification, such as the polymerase chain reaction, the specificity of primers selected combined with the amplification of the CMV template would render contaminating infectious agents undetectable in this system.

The third general issue raised in the Office Action concerns ex vivo methods in which blood is withdrawn from a patient, with the Office Action noting several specific concerns with respect to this general issue. The Office Action first states that the specification does not describe how much blood is necessary to determine the presence or absence of mutations. It is initially noted that the specification "need not teach, and preferably omits, what is well known in the art" (see MPEP 2164.01; see also *In re Buchner* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1988). As already pointed out, methods for analyzing nucleic acids for the presence or absence of mutations was known as of the priority date of the instant application (see, e.g., methods listed at page 22, lines 5-9), including how much sample is necessary to conduct a given analysis. Those in the art would have recognized that many nucleic acid analyses could be conducted with minute quantities of blood. Thus, in some methods, only very small amounts of blood are required.

The Office Action also contends that the specification does not describe how to compensate for the loss of blood when blood is continuously withdrawn. To reiterate the point just made, however, the currently claimed methods in some instances can be performed with very small amounts of blood, thus rendering this issue moot. Even if larger quantities of blood were withdrawn, the application describes a system for returning the blood (see, e.g., page 15,

line 23 to page 17, line 24. A variety of methods for recirculating withdrawn blood back into a patient were known, including in the fields of dialysis and phoresis as of the priority date of the application (see, e.g., U.S. Patent Nos. 4,711,715 and 4,894,164; copies enclosed).

With respect to the assertion that the specification does not describe how to extract CMV or CVM-infected cells from the compound in the collector, it is first noted that it is not necessary to do this for a number of nucleic acid analysis methods (e.g. PCR). Even if necessary, extraction could be achieved by competing the CMV or CMV-infected cells from the compound with a large excess of compound or other ligand that binds CMV.

The final issue raised with respect to ex vivo methods is that the specification allegedly does not describe how to prevent compound that did not bind CMV from entering the patient and potentially disrupting the patient's blood chemistry. In those instances in which this was considered to be a potential issue, the specification discusses facile solutions, namely use of a container that retains the compound and/or immobilizing the compound to a support to prevent transfer of compound to the patient (see, e.g., page 16, line 25 to page 17, line 4).

The fourth general issue presented in the Office Action includes several specific concerns with respect to methods that use an implant device to collect CMV or CMV-infected cells. The Office Action states, for instance, that the specification does not describe how long the implant device should be left in place to collect sufficient CMV or CMV-infected cells. As already noted, however, many nucleic acid analyses can be conducted with minute quantities of sample. It is thus expected that in many instances that the implant would only need to be left in for relatively short periods.

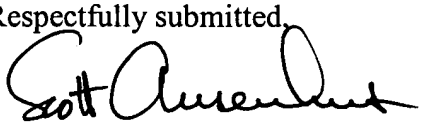
On page 8, the possibility that the CMV-binding compound might affect the blood chemistry of the patient is again raised. The Office Action in particular notes that some of the cited compounds have anti-psychotic effects. In response, it is noted that the specification discusses the option of immobilizing the compound to a support that is part of the implant device (see, e.g., page 14, lines 30-32; see also page 16, line 33 to page 17, line 4). Immobilization in this way would address this concern. Furthermore, octociothepin maleate, the anti-psychotic compound specifically referred to in the Office Action, has been known since the late 1960's (see enclosed entries from the 12 edition of the Merck Index and Sigma catalog), and there is a

significant literature on this compound, including toxicity, efficacy and safety data in mice, rats and humans. Thus, one of ordinary skill in the art would be able to evaluate any potential risks and could monitor the presence of this compound and adjust treatment in accordance with the toxicity and safety data that has long been available on this particular compound.

It is thus submitted that the foregoing reasons fully address the enablement concerns raised in the Office Action. Accordingly, it is requested that the enablement rejection be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



Scott L. Ausenhus
Reg. No. 42,271

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 303-571-4000
Fax: 415-576-0300
SLA:tnd
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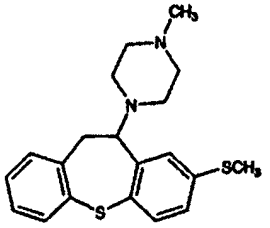
Merck Index, 12th Edition

6222. Metitepine. *1-[10,11-Dihydro-8-(methylthio)dibenzo[b,f]thiepin-10-yl]-4-methylpiperazine;* 8-methylthio-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepine; methiothepine; methiothepin; Ro-8-6837. $C_{20}H_{24}N_2S_2$; mol wt 356.56. C 67.37%, H 6.78%, N 7.86%, S 17.99%. Serotonin (5-HT_2) receptor antagonist; also exhibits affinity for 5-HT_1-receptors. Prepn: Neth. pat. Appl. 6,608,618; M. Protiva *et al.*, U.S. pat. 3,379,729 (1966, 1968 both to SPOFA); and pharmacology: K. Pelz *et al.*, *Coll. Czech. Chem. Commun.* **33**, 1895 (1968); J. O. Jilek *et al.*, *ibid.* **39**, 3338 (1974). Receptor-blocking study: M.-A. Monachon *et al.*, *Arch. Pharmacol.* **274**, 192 (1972). Use in classification of 5-HT receptors: P. B. Bradley *et al.*, *Neuropharmacology* **25**, 563 (1986); E. J. Mylecharane, *Clin. Exp. Pharmacol. Physiol.* **16**, 517 (1989).



Crystals from ethanol, mp 88-89°.

Maleate, $C_{20}H_{24}N_2S_2 \cdot C_4H_4O_4$, crystals from ethanol, mp 171-173°. LD_{50} in mice (mg/kg): 51 i.v.; 94 orally (Jilek).

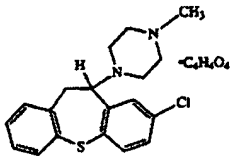
USE: Biochemical tool in serotonin receptor binding studies.

Sigma - RBI Catalog 1999

Octoclothepin maleate — 25 mg 29.00; 100 mg 85.00

D_2 Dopamine receptor antagonist; serotonin receptor antagonist.

1-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yl)-4-methyl-piperazine maleate Mol. Wt. 460.98 $C_{19}H_{21}ClN_2S \cdot C_4H_4O_4$ [4789-68-8] Disposal A. White solid; mp 203-204°C. Store tightly sealed at RT. Slightly soluble in water or methanol. Solubility in 45% (w/v) aqueous 2-hydroxypropyl-β-cyclodextrin (Cat. No. H-107): > 21 mg/ml.



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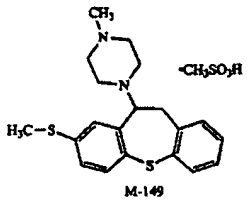
Hyttel et al. "Characterization of binding of ^{3}H-SCH 23390 to dopamine D_1 receptors. Correlation to other D-1 and D-2 measures and effect of selective lesions." *J. Neural Trans.* **68**, 171 (1987); Nakajima et al. "[^{3}H]Ro 22-1319 (piquindone) binds to the D_2 dopaminergic receptor subtype in a sodium-dependent manner." *Mol. Pharmacol.* **26**, 430 (1984); Wang Lu et al. "Effects of various neuroleptics, phenobarbital and SKF 525-A on dimethyltryptamine content in rat brain and liver." *Arch. Int. Pharmacodyn. Ther.* **232**, 117 (1978).

Methiothepin mesylate — 100 mg 40.00; 250 mg 81.00
Metitepine mesylate

5-HT_1 Serotonin receptor antagonist; blocks serotonin autoreceptors.

1-[10,11-Dihydro-8-(methylthio)dibenzo[b,f]thiepin-10-yl]-4-methylpiperazine mesylate Mol. Wt. 452.64 $C_{20}H_{24}N_2S_2 \cdot CH_3SO_3H$ [20229-30-5 (free base)] Disposal A. White solid; mp 188-190°C. Store tightly sealed at RT. Soluble in water (13 mg/ml).



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Martin et al. "Comparison of the pharmacological characteristics of $5HT_1$ and $5HT_2$ binding sites with those of serotonin autoreceptors which modulate serotonin release." *Naunyn-Schmiedeberg's Arch. Pharmacol.* **321**, 165-170 (1982); Nelson et al. "*In vitro* and *in vivo* disposition of [^{3}H]-Methiothepin in brain tissues." *Ibid* **310**, 25-33 (1979); Pettibone et al. "Effects of methiothepin and lysergic acid diethylamide on serotonin release *in vitro* and serotonin synthesis *in vivo*: Possible relation to serotonin autoreceptor function." *J. Neurochem.* **43**, 83-90 (1984).